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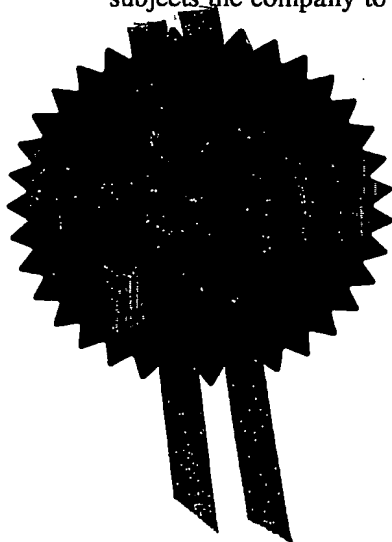
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2. Patent application number (The Patent office will fill in this part)	06 AUG 2002		
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Patents ADP number (if you know it)	00443587003		
If the applicant is a corporate body, give the country/state of its corporation	GB		
4. Title of the invention	ANTIBODIES		
5. Name of your agent (if you know one)	STEPHANIE A. LEAROYD		
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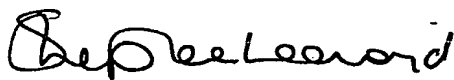
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I/We request the grant of a patent on the basis of this application



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AntibodiesField of the Invention

The present invention relates to humanised antibodies that bind to myelin associated glycoprotein (MAG) and polynucleotides encoding same, pharmaceutical  
10 formulations containing them and to the use of such antibodies in the treatment and/or prophylaxis of neurological diseases.

Background of the Invention

Stroke is a major cause of death and disability in the Western World. There is no  
15 approved therapy for the treatment of stroke other than t-PA which has to be administered within 3h of onset following a CT scan to exclude haemorrhage. To date most therapeutic agents directed towards the treatment of acute stroke (i.e. neuroprotection), have predominantly involved targeting glutamate receptors and their  
20 down stream signalling pathways known to be involved in acute cell death. However to date these strategies have proved unsuccessful in clinical trials and are often associated with dose-limiting side effects (Hill & Hachinski, The Lancet, 352 : (suppl III) 10-14 (1998)). Therefore there is a need for novel approaches directed towards the amelioration of cell death following the cessation of blood flow.

Following the onset of stroke, some degree of spontaneous functional recovery is  
25 observed in many patients, suggesting that the brain has the (albeit limited) ability to repair and/or remodel following injury. Agents that have the potential to enhance this recovery may therefore allow intervention to be made much later (potentially days) following the onset of cerebral ischaemia. Agents which are able to offer both acute neuroprotection and enhance functional recovery may provide significant advantages  
30 over current potential neuroprotective strategies.

The mechanisms underlying functional recovery are currently unknown. The sprouting of injured or non-injured axons has been proposed as one possible mechanism. However, although *in vivo* studies have shown that treatment of spinal cord injury or stroke with neurotrophic factors results in enhanced functional recovery and a degree of  
35 axonal sprouting, these do not prove a direct link between the degree of axonal sprouting and extent of functional recovery (Jakeman, et al. 1998, Exp. Neurol. 154 : 170-184,

- 5 Kawamata et al. 1997, Proc Natl Acad. Sci. USA., 94:8179-8184, Ribotta, et al. 2000, J Neurosci. 20 : 5144-5152). Furthermore, axonal sprouting requires a viable neuron. In diseases such as stroke which is associated with extensive cell death, enhancement of functional recovery offered by a given agent post stroke may therefore be through mechanisms other than axonal sprouting such as differentiation of endogenous stem
- 10 cells, activation of redundant pathways, changes in receptor distribution or excitability of neurons or glia (Fawcett & Asher, 1999, Brain Res. Bulletin, 49 : 377-391, Horner & Gage, 2000, Nature 407 963-970).

The limited ability of the central nervous system (CNS) to repair following injury is thought in part to be due to molecules within the CNS environment that have an

15 inhibitory effect on axonal sprouting (neurite outgrowth). CNS myelin is thought to contain inhibitory molecules (Schwab ME and Caroni P (1988) *J. Neurosci.* 8, 2381-2193). Two myelin proteins, myelin-associated glycoprotein (MAG) and Nogo have been cloned and identified as putative inhibitors of neurite outgrowth (Sato S. et al (1989) *Biochem. Biophys. Res. Comm.* 163, 1473-1480; McKerracher L et al (1994) *Neuron* 13, 805-811;

20 Mukhopadhyay G et al (1994) *Neuron* 13, 757-767; Torigoe K and Lundborg G (1997) *Exp. Neurology* 150, 254-262; Schafer et al (1996) *Neuron* 16, 1107-1113; WO9522344; WO9701352; Prinjha R et al (2000) *Nature* 403, 383-384; Chen MS et al (2000) *Nature* 403, 434-439; GrandPre T et al (2000) *Nature* 403, 439-444; US005250414A; WO200005364A1; WO0031235).

25 Myelin-associated glycoprotein is a cell surface transmembrane molecule expressed on the surface of myelin consisting of five extracellular immunoglobulin domains, a single transmembrane domain and an intracellular domain. MAG expression is restricted to myelinating glia in the CNS and peripheral nervous system (PNS). MAG is thought to interact with neuronal receptor(s) which mediate effects on the neuronal

30 cytoskeleton including neurofilament phosphorylation and inhibition of neurite outgrowth *in vitro*. Although antagonists of MAG have been postulated as useful for the promotion of axonal sprouting following injury (WO9522344, WO9701352 and WO9707810), these claims are not supported by *in vivo* data. Furthermore, the role of MAG as an inhibitor of axonal sprouting from CNS neurons *in vivo* is not proven (Li CM et

35 al (1994) *Nature* 369, 747-750; Montag, D et al (1994) *Neuron* 13, 229-246; Lassmann H et al (1997) *GLIA* 19, 104-110; Li C et al (1998) *J. Neuro. Res.* 51, 210-217; Yin X et al

- 5 (1998) *J. Neurosci.* 18, 1953-1962; Bartsch U et al (1995) *Neuron* 15 1375-1381; Li M et al (1996) 46,404-414).

Antibodies typically comprise two heavy chains linked together by disulphide bonds and two light chains. Each light chain is linked to a respective heavy chain by disulphide bonds. Each heavy chain has at one end a variable domain followed by a  
10 number of constant domains. Each light chain has a variable domain at one end and a constant domain at its other end. The light chain variable domain is aligned with the variable domain of the heavy chain. The light chain constant domain is aligned with the first constant domain of the heavy chain. The constant domains in the light and heavy chains are not involved directly in binding the antibody to antigen.

15 The variable domains of each pair of light and heavy chains form the antigen binding site. The domains on the light and heavy chains have the same general structure and each domain comprises a framework of four regions, whose sequences are relatively conserved, connected by three complementarity determining regions (CDRs) often referred to as hypervariable regions. The four framework regions largely adopt a beta-  
20 sheet conformation and the CDRs form loops connecting, and in some cases forming part of, the beta-sheet structure. The CDRs are held in close proximity by the framework regions and, with the CDRs from the other domain, contribute to the formation of the antigen binding site. CDRs and framework regions of antibodies may be determined by reference to Kabat et al ("Sequences of proteins of immunological interest" US Dept. of  
25 Health and Human Services, US Government Printing Office, 1987).

It has now been found that an anti-MAG monoclonal antibody, described (Poltorak et al (1987) *Journal of Cell Biology* 105,1893-1899, DeBellard et al (1996) *Mol. Cell. Neurosci.* 7, 89-101; Tang et al (1997) *Mol. Cell. Neurosci.* 9, 333-346; Torigoe K and Lundborg G (1997) *Exp. Neurology* 150, 254-262) and commercially available (MAB1567  
30 (Chemicon)) when administered either directly into the brain or intravenously following focal cerebral ischaemia in the rat (a model of stroke), provides neuroprotection and enhances functional recovery. Therefore anti-MAG antibodies provide potential therapeutic agents for both acute neuroprotection as well as the promotion of functional recovery following stroke. This antibody is a murine antibody. Although murine  
35 antibodies are often used as diagnostic agents their utility as a therapeutic has been proven in only a few cases. Their limited application is in part due to the repeated

5 administration of murine monoclonals to humans usually elicits human immune responses against these molecules. To overcome these intrinsic undesirable properties of murine monoclonals, "altered" antibodies designed to incorporate regions of human antibodies have been developed. For example, a humanised antibody contains complementarity determining regions ("CDR's") of non human origin and the majority of  
10 the rest of the structure is derived from a human antibody.

The process of neurodegeneration underlies many neurological diseases including acute diseases such as stroke, traumatic brain injury and spinal cord injury as well as chronic diseases including Alzheimer's disease, fronto-temporal dementias (tauopathies), peripheral neuropathy, Parkinson's disease, Huntington's disease and multiple sclerosis.  
15 Anti-MAG mabs therefore may be useful in the treatment of these diseases, by both ameliorating the cell death associated with these disorders and promoting functional recovery.

#### Brief Summary of the Invention

20 The invention provides a humanised antibody or functional fragment thereof that binds to and neutralises MAG which comprises a heavy chain variable region comprising the following amino acid sequence

25 QVQLVQSGSELKKPGASVKVSCASGYTFTNYGMNWVRQAPGQGLEWMGWI  
NTYTGEPTYADDFTGRFVFSLDTSVSTAYLQISSLKAEDTAVYYCARNPIN  
YYGINYEGYVMDYWGQTLTVSS (SEQ ID No 1).

In a further aspect of the invention there is provided a humanised antibody or functional fragment thereof which binds to MAG which comprises the heavy chain  
30 variable region of Sequence ID No 1 together with a light chain variable region comprising from amino acid Sequence ID No 2,3,4 or 5:

35 DIVMTQSPDSLAVSLGERATINCKSSHSVLYSSNQKNYLAWYQQKPGQPPK  
LLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCHQYLSSLT  
FGQGTKLEIKRTV (SEQ ID No 2)

5

DIVMTQSPDSLAVSLGERATINCKSSH~~SVLYSSNQKNYLAWYQQKPGQPPK~~  
 LLIYWASTRESGVPDRFSGSGSGTDFTLTIIINLQAEDVAVYYCHQYLS~~SLT~~  
 FGQGTKLEIKRTV (SEQ ID No 3)

10

15 DIVMTQSPDSLAVSLGERATINCKSSH~~SVLYSSNQKNYLAWYQQKPGQPPK~~  
 LLIYWASTRESGVPDRFSGSGSGTDFTLTIIINLHTEDVAVYYCHQYLS~~SLT~~  
 FGQGTKLEIKRTV (SEQ ID No 4)

20

DIVMTQSPDSLAVSLGERATINCKSSH~~SVLYSSNQKNYLAWYQQKPGQPPK~~  
 LLIYWASTRESGVPDRFSGSGSGTDFTLTIIINLHTEDVAVYYCHQYLS~~SLT~~  
 FGQGTKLEIKRTV (SEQ ID No 5)

25

In a further aspect of the present invention there is provided a humanised antibody comprising:

a heavy chain variable fragment comprising SEQ ID No 1 and a constant part or fragment thereof of a human heavy chain

30

and

a light chain variable fragment comprising SEQ ID No 2, 3, 4 or 5 and a constant part or fragment thereof of a human light chain.

A further aspect of the invention provides a pharmaceutical composition comprising a humanised anti-MAG antibody of the present invention or functional fragment thereof together with a pharmaceutically acceptable diluent or carrier.

In a further aspect, the present invention provides a method of treatment or prophylaxis of stroke and other neurological diseases in a human which comprises administering to said human in need thereof an effective amount of an anti-MAG antibody of the invention functional fragments thereof.



5 In another aspect, the invention provides the use of an anti-MAG antibody of the invention or a functional fragment thereof in the preparation of a medicament for treatment or prophylaxis of stroke and other neurological diseases.

In a further aspect, the present invention provides a method of inhibiting neurodegeneration and/or promoting functional recovery in a human patient suffering, or  
10 at risk of developing, a stroke or other neurological disease which comprises administering to said human in need thereof an effective amount of an anti-MAG antibody of the invention or a functional fragment thereof.

In a yet further aspect, the invention provides the use of an anti-MAG antibody, of the invention or a functional fragment thereof in the preparation of a medicament for  
15 inhibiting neurodegeneration and/or promoting functional recovery in a human patient suffering from, or at risk of developing, a stroke and other neurological disease.

Other aspects and advantages of the present invention are described further in the detailed description and the preferred embodiments thereof.

## 20 Detailed Description of the Invention

A humanized antibody refers to a type of antibody having its CDRs derived from a non-human donor immunoglobulin (donor antibody), the remaining immunoglobulin-derived parts of the molecule being derived from one (or more) human immunoglobulin(s)  
25 (acceptor antibody). In addition, framework support residues may be altered to preserve binding affinity (see, e.g., Queen et al., *Proc. Natl Acad Sci USA*, **86**:10029-10032 (1989), Hodgson et al., *Bio/Technology*, **9**:421 (1991)). A suitable human acceptor antibody may be one selected from a conventional database, e.g., the KABAT® database, Los Alamos database, and Swiss Protein database, by homology to the nucleotide and amino acid  
30 sequences of the donor antibody. A human antibody characterized by a homology to the framework regions of the donor antibody (on an amino acid basis) may be suitable to, provide a heavy chain constant region and/or a heavy chain variable framework region for insertion of the donor CDRs. A suitable acceptor antibody capable of donating light chain constant or variable framework regions may be selected in a similar manner. It should be  
35 noted that the acceptor antibody heavy and light chains are not required to originate from the same acceptor antibody.

5 Desirably the heterologous framework and constant regions are selected from human immunoglobulin classes and isotypes, such as IgG (subtypes 1 through 4), IgM, IgA, and IgE. However, the acceptor antibody need not comprise only human immunoglobulin protein sequences. For instance a gene may be constructed in which a DNA sequence encoding part of a human immunoglobulin chain is fused to a DNA sequence encoding a  
10 non-immunoglobulin amino acid sequence such as a polypeptide effector or reporter molecule.

The constant region domains comprise suitable human constant domain regions for example, see Kabat, Sequences of proteins of immunological interest, US Department of Health and Human Services, Public Health Service, National Institute of Health. The  
15 humanised antibody preferably has the structure of a natural antibody or fragment thereof. The antibody may therefore comprise a complete antibody, a (Fab')<sub>2</sub> fragment, a Fab fragment, a light chain dimer or a heavy chain dimer. The antibody may be an IgG1, IgG2, IgG3, or IgG4; or IgM; IgA, IgE or IgD or a modified variant thereof. The constant domain of the antibody heavy chain may be selected accordingly. The light chain  
20 constant domain may be a kappa or lambda constant domain.

The constant region is selected according to the functionality required. Normally an IgG1 will demonstrate lytic ability through binding to complement and will mediate ADCC (antibody dependent cell cytotoxicity). An IgG4 will be preferred if a non-cytotoxic blocking antibody is required. However, IgG4 antibodies can demonstrate  
25 instability in production and therefore it may be more preferable to modify the generally more stable IgG1. Suggested modifications are described in EPO307434 preferred modifications include at positions 235 and 237. The invention therefore provides a lytic or a non-lytic form of an antibody according to the invention.

30 In a preferred aspect the altered antibody is class IgG, more preferably IgG1.

Preferred antibodies of the present invention comprise:

Heavy chain variable region comprising Seq ID No 1 and light chain variable region comprising Seq ID No 2;

35 Heavy chain variable region comprising Seq ID No 1 and light chain variable region comprising Seq ID No 3;

5 Heavy chain variable region comprising Seq ID No 1 and light chain variable region comprising Seq ID No 4;

Heavy chain variable region comprising Seq ID No 1 and light chain variable region comprising Seq ID No 5.

10 In a further aspect, the invention provides polynucleotides encoding the heavy chain variable region comprising Sequence ID No 1 and light chain variable regions comprising Sequence ID No 2,3,4 or 5.

Preferred polynucleotide sequence encoding the amino acid Sequence ID No 1 is:

15 CAGGTGCAGCTGGTGCAATCTGGGTCTGAGTTGAAGAAGCCTGGGGCCTCA  
GTGAAGGTTTCCTGCAAGGCTTCTGGATACACCTTCACTAACTACGGCATG  
AACTGGGTGCGACAGGCCCTGGACAAGGGCTTGAGTGGATGGGATTGGATC  
AACACCTACACGGCGAGCCACCTACGCCGACGACTTCACCGGCCGGTTT  
GTCTTCTCCTTGGACACCTCTGTCAGCACGGCATATCTGCAGATCAGCAGC  
CTAAAGGCTGAGGACACTGCCGTGTATTACTGTGCGAGAAACCCCATCAAC  
20 TACTACGGCATCAACTACGAGGGCTACGTGATGGACTACTGGGGCCAGGGC  
ACACTAGTCACAGTCTCCTCA (SEQ ID No 6)

Preferred polynucleotide sequence encoding amino acid SEQ ID No 2 is:

25 GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAG  
AGGGCCACCATCAACTGCAAAGAGCAGCCACAGCGTGCTGTACAGCAGCAAC  
CAGAAGAACTACCTGGCCTGGTACCAGCAGAAACCAGGACAGCCTCCTAAG  
CTGCTCATTTACTTGGGCATCTACCCGGGAATCCGGGGTCCCTGACCGATTCT  
30 AGTGGCAGCGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAG  
GCTGAAGATGTGGCAGTTTATTACTGTCACCAGTACCTGAGCAGCCTGACC  
TTTGGCCAGGGGACCAAGCTGGAGATCAAACGTACGGTG (SEQ ID No  
7)

35 Preferred polynucleotide sequence encoding SEQ ID No 3 is:

40 GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAG  
AGGGCCACCATCAACTGCAAAGAGCAGCCACAGCGTGCTGTACAGCAGCAAC  
CAGAAGAACTACCTGGCCTGGTACCAGCAGAAACCAGGACAGCCTCCTAAG  
CTGCTCATTTACTTGGGCATCTACCCGGGAATCCGGGGTCCCTGACCGATTCT  
AGTGGCAGCGGGTCTGGGACAGATTTCACTCTCACCATCATCAACCTGCAG  
GCTGAAGATGTGGCAGTTTATTACTGTCACCAGTACCTGAGCAGCCTGACC

5 TTTGGCCAGGGGACCAAGCTGGAGATCAAACGTACGGTG (SEQ ID No 8)

Preferred polynucleotide encoding SEQ ID No 4 is:

10 GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAG  
 AGGGCCACCATCAACTGCAAGAGCAGCCACAGCGTGCTGTACAGCAGCAAC  
CAGAAGAACTACCTGGCCTGGTACCAGCAGAAACCAGGACAGCCTCCTAAG  
 CTGCTCATTCTACTGGGCATCTACCCGGGAATCCGGGGTCCCTGACCGATTC  
 15 AGTGGCAGCGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAC  
ACCGAAGATGTGGCAGTTTATTACTGTCAACAGTACCTGAGCAGCCTGACC  
 TTTGGCCAGGGGACCAAGCTGGAGATCAAACGTACGGTG (SEQ ID No 9)

20 Preferred polynucleotide encoding SEQ ID No 5 is:

GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAG  
 AGGGCCACCATCAACTGCAAGAGCAGCCACAGCGTGCTGTACAGCAGCAAC  
 25 CAGAAGAACTACCTGGCCTGGTACCAGCAGAAACCAGGACAGCCTCCTAAG  
 CTGCTCATTCTACTGGGCATCTACCCGGGAATCCGGGGTCCCTGACCGATTC  
 AGTGGCAGCGGGTCTGGGACAGATTTCACTCTCACCATCATCAACCTGCAC  
ACCGAAGATGTGGCAGTTTATTACTGTCAACAGTACCTGAGCAGCCTGACC  
 TTTGGCCAGGGGACCAAGCTGGAGATCAAACGTACGGTG (SEQ ID No 10)

"Neutralising" refers to substantial inhibition of MAG function including its binding to neurones and inhibition of neurite outgrowth.

35 "Substantial inhibition" refers to 75%, more preferably 85%, most preferably 95% inhibition measured in *in vitro* tests.

"Altered immunoglobulin coding region" refers to a nucleic acid sequence encoding humanised antibody. The sequences that encode the complementarity determining regions (CDRs) from a non-human immunoglobulin are inserted into a first  
 40 immunoglobulin partner comprising human variable framework sequences. Optionally, the first immunoglobulin partner is operatively linked to a second immunoglobulin partner.

5 "First immunoglobulin partner" refers to a nucleic acid sequence encoding a human framework or human immunoglobulin variable region in which the native (or naturally-occurring) CDR-encoding regions are replaced by the CDR-encoding regions of a donor antibody. The human variable region can be an immunoglobulin heavy chain, a light chain (or both chains), an analog or functional fragments thereof. Such CDR  
10 regions, located within the variable region of antibodies (immunoglobulins) can be determined by known methods in the art. For example Kabat et al. (Sequences of Proteins of Immunological Interest, 4th Ed., U.S. Department of Health and Human Services, National Institutes of Health (1987)) disclose rules for locating CDRs. In addition, computer programs are known which are useful for identifying CDR regions/structures.

15 "Second immunoglobulin partner" refers to another nucleotide sequence encoding a protein or peptide to which the first immunoglobulin partner is fused in frame or by means of an optional conventional linker sequence (i.e., operatively linked). Preferably it is an immunoglobulin gene. The second immunoglobulin partner may include a nucleic acid sequence encoding the entire constant region for the same (i.e., homologous - the  
20 first and second altered antibodies are derived from the same source) or an additional (i.e., heterologous) antibody of interest. It may be an immunoglobulin heavy chain or light chain (or both chains as part of a single polypeptide). The second immunoglobulin partner is not limited to a particular immunoglobulin class or isotype. In addition, the second immunoglobulin partner may comprise part of an immunoglobulin constant  
25 region, such as found in a Fab, or F(ab)<sub>2</sub> (i.e., a discrete part of an appropriate human constant region or framework region). Such second immunoglobulin partner may also comprise a sequence encoding an integral membrane protein exposed on the outer surface of a host cell, e.g., as part of a phage display library, or a sequence encoding a protein for analytical or diagnostic detection, e.g., horseradish peroxidase,  $\beta$ -  
30 galactosidase, etc.

The terms Fv, Fc, Fd, Fab, or F(ab)<sub>2</sub> are used with their standard meanings (see, e.g., Harlow et al., Antibodies A Laboratory Manual, Cold Spring Harbor Laboratory, (1988)).

A "vectored antibody" refers to an antibody to which an agent has been attached to improve transport through the blood brain barrier (BBB). The attachment may be  
35 chemical or alternatively the moiety can be engineered into the antibody. One example is to make a chimera with an antibody directed towards a brain capillary endothelial cell

- 5 receptor eg an anti-insulin receptor antibody or anti-transferrin receptor antibody (Saito et al (1995) *Proc. Natl. Acad. Sci. USA* 92 10227-31; Pardridge et al (1995) *Pharm. Res.* 12 807-816; Broadwell et al (1996) *Exp. Neurol.* 142 47-65; Bickel et al (1993) *Proc Natl. Acad. Sci. USA* 90, 2618-2622; Friden et al (1996) *J. Pharm. Exp. Ther.* 278 1491-1498, US5182107, US5154924, US5833988, US5527527). Once bound to the receptor, both
- 10 components of the bispecific antibody pass across the BBB by the process of transcytosis. Alternatively the agent may be a ligand which binds such cell surface receptors eg insulin, transferrin or low density lipoprotein (Descamps et al (1996) *Am. J. Physiol.* 270 H1149-H1158; Duffy et al (1987) *Brain Res.* 420 32-38; Dehouck et al (1997) *J. Cell Biol.* 1997 877-889). Naturally occurring peptides such as penetratin and SynB1 and Syn B3 which
- 15 are known to improve transport across the BBB can also be used (Rouselle et al (2000) *Mol. Pharm.* 57, 679-686 and Rouselle et al (2001) *Journal of Pharmacology and Experimental Therapeutics* 296, 124-131).

The term "donor antibody" refers to an antibody (monoclonal, or recombinant) which contributes the amino acid sequences of its variable regions, CDRs, or other

20 functional fragments or analogs thereof to a first immunoglobulin partner, so as to provide the altered immunoglobulin coding region and resulting expressed altered antibody with the antigenic specificity and neutralizing activity characteristic of the donor antibody.

The term "acceptor antibody" refers to an antibody (monoclonal, or recombinant)

25 heterologous to the donor antibody, which contributes all (or any portion, but preferably all) of the amino acid sequences encoding its heavy and/or light chain framework regions and/or its heavy and/or light chain constant regions to the first immunoglobulin partner. Preferably a human antibody is the acceptor antibody.

"CDRs" are defined as the complementarity determining region amino acid sequences

30 of an antibody which are the hypervariable regions of immunoglobulin heavy and light chains. See, e.g., Kabat et al., Sequences of Proteins of Immunological Interest, 4th Ed., U.S. Department of Health and Human Services, National Institutes of Health (1987). There are three heavy chain and three light chain CDRs (or CDR regions) in the variable portion of an immunoglobulin. Thus, "CDRs" as used herein refers to all three heavy chain

35 CDRs, or all three light chain CDRs (or both all heavy and all light chain CDRs, if appropriate). The structure and protein folding of the antibody may mean that other

5 residues are considered part of the antigen binding region and would be understood to be so by a skilled person. See for example Chothia et al., (1989) Conformations of immunoglobulin hypervariable regions; Nature 342, p877-883. For convenience the CDR's as defined by Kabat in SEQ ID Nos 1 - 5 are underlined.

CDRs provide the majority of contact residues for the binding of the antibody to  
10 the antigen or epitope. CDRs of interest in this invention are derived from donor antibody variable heavy and light chain sequences, and include analogs of the naturally occurring CDRs, which analogs also share or retain the same antigen binding specificity and/or neutralizing ability as the donor antibody from which they were derived.

A "functional fragment" is a partial heavy or light chain variable sequence (e.g.,  
15 minor deletions at the amino or carboxy terminus of the immunoglobulin variable region) which retains the same antigen binding specificity and/or neutralizing ability as the antibody from which the fragment was derived.

An "analog" is an amino acid sequence modified by at least one amino acid, wherein said modification can be chemical or a substitution or a rearrangement of a few  
20 amino acids (i.e., no more than 10), which modification permits the amino acid sequence to retain the biological characteristics, e.g., antigen specificity and high affinity, of the unmodified sequence. For example, (silent) mutations can be constructed, via substitutions, when certain endonuclease restriction sites are created within or surrounding CDR-encoding regions. The present invention contemplates the use of  
25 analogs of the antibodies of the invention. It is well known that minor changes in amino acid or nucleic acid sequences may lead eg to an allelic form of the original protein which retains substantially similar properties. Thus analogs of the antibody of the invention includes those in which the CDRs in the hypervariable region of the heavy and light chains are at least 80% homologous, preferably at least 90 % homologous and more  
30 preferably at least 95% homologous to the CDRs as defined above and retain MAG neutralising activity. The invention also contemplates analogs of the antibodies of the invention wherein the framework regions are at least 80%, preferably at least 90% and more preferably at least 95% homologous to the framework regions set forth in Seq ID 1 - 5. Amino acid sequences are at least 80% homologous if they have 80% identical  
35 amino acid residues in a like position when the sequences are aligned optimally, gaps or insertions being counted as non-identical residues.

5           Analogues may also arise as allelic variations. An "allelic variation or modification" is an alteration in the nucleic acid sequence. Such variations or modifications may be due to degeneracy in the genetic code or may be deliberately engineered to provide desired characteristics. These variations or modifications may or may not result in alterations in any encoded amino acid sequence.

10           The term "effector agents" refers to non-protein carrier molecules to which the humanised antibodies, and/or natural or synthetic light or heavy chains of the donor antibody or other fragments of the donor antibody may be associated by conventional means. Such non-protein carriers can include conventional carriers used in the diagnostic field, e.g., polystyrene or other plastic beads, polysaccharides, e.g., as used in the BIAcore  
15 [Pharmacia] system, or other non-protein substances useful in the medical field and safe for administration to humans and animals. Other effector agents may include a macrocycle, for chelating a heavy metal atom, or radioisotopes. Such effector agents may also be useful to increase the half-life of the altered antibodies, e.g., polyethylene glycol.

          The present invention also includes the use of Fab fragments or F(ab')<sub>2</sub> fragments  
20 derived from mAbs directed against MAG. These fragments are useful as agents protective *in vivo*. A Fab fragment contains the entire light chain and amino terminal portion of the heavy chain; and an F(ab')<sub>2</sub> fragment is the fragment formed by two Fab fragments bound by disulfide bonds. Fab fragments and F(ab')<sub>2</sub> fragments can be obtained by conventional means, e.g., cleavage of mAb with the appropriate proteolytic  
25 enzymes, papain and/or pepsin, or by recombinant methods. The Fab and F(ab')<sub>2</sub> fragments are useful themselves as therapeutic or prophylactic, and as donors of sequences including the variable regions and CDR sequences useful in the formation of recombinant or humanized antibodies as described herein.

          The Fab and F(ab')<sub>2</sub> fragments can also be constructed via a combinatorial phage  
30 library (see, e.g., Winter et al., Ann. Rev. Immunol., 12:433-455 (1994)) or via immunoglobulin chain shuffling (see, e.g., Marks et al., Bio/Technology, 10:779-783 (1992), which are both hereby incorporated by reference in their entirety.

          Thus human antibody fragments (Fv, scFv, Fab) specific for MAG can be isolated using human antibody fragment phage display libraries. A library of bacteriophage  
35 particles, which display the human antibody fragment proteins, are panned against the MAG protein. Those phage displaying antibody fragments that bind the MAG are retained



5 from the library and clonally amplified. The human antibody genes are then excised from the specific bacteriophage and inserted into human IgG expression constructs containing the human IgG constant regions to form the intact human IgG molecule with the variable regions from the isolated bacteriophage specific for MAG.

10 The donor antibodies may contribute sequences, such as variable heavy and/or light chain peptide sequences, framework sequences, CDR sequences, functional fragments, and analogs thereof, and the nucleic acid sequences encoding them, useful in designing and obtaining various altered antibodies which are characterized by the antigen binding specificity of the donor antibody.

Taking into account the degeneracy of the genetic code, various coding sequences  
15 may be constructed which encode the variable heavy and light chain amino acid sequences, and CDR sequences as well as functional fragments and analogs thereof which share the antigen specificity of the donor antibody. Isolated nucleic acid sequences, or fragments thereof, encoding the variable chain peptide sequences or CDRs can be used to produce altered antibodies, e.g., chimeric or humanized antibodies, or other engineered  
20 antibodies when operatively combined with a second immunoglobulin partner.

Preferably, the first immunoglobulin partner is operatively linked to a second immunoglobulin partner. The second immunoglobulin partner is defined above, and may include a sequence encoding a second antibody region of interest, for example an Fc region. Second immunoglobulin partners may also include sequences encoding another  
25 immunoglobulin to which the light or heavy chain constant region is fused in frame or by means of a linker sequence. Engineered antibodies directed against functional fragments or analogs of MAG may be designed to elicit enhanced binding.

The second immunoglobulin partner may also be associated with effector agents as defined above, including non-protein carrier molecules, to which the second  
30 immunoglobulin partner may be operatively linked by conventional means.

Fusion or linkage between the second immunoglobulin partners, e.g., antibody sequences, and the effector agent may be by any suitable means, e.g., by conventional covalent or ionic bonds, protein fusions, or hetero-bifunctional cross-linkers, e.g., carbodiimide, glutaraldehyde, and the like. Such techniques are known in the art and  
35 readily described in conventional chemistry and biochemistry texts.

5           Additionally, conventional linker sequences which simply provide for a desired amount of space between the second immunoglobulin partner and the effector agent may also be constructed into the altered immunoglobulin coding region. The design of such linkers is well known to those of skill in the art.

10           In still a further embodiment, the antibody of the invention may have attached to it an additional agent. For example, the procedure of recombinant DNA technology may be used to produce an engineered antibody of the invention in which the Fc fragment or CH2-CH3 domain of a complete antibody molecule has been replaced by an enzyme or other detectable molecule (i.e., a polypeptide effector or reporter molecule).

15           The second immunoglobulin partner may also be operatively linked to a non-immunoglobulin peptide, protein or fragment thereof heterologous to the CDR-containing sequence having the antigen specificity of anti-MAG antibody. The resulting protein may exhibit both anti-MAG antigen specificity and characteristics of the non-immunoglobulin upon expression. That fusion partner characteristic may be, e.g., a functional characteristic such as another binding or receptor domain, or a therapeutic characteristic if the fusion partner is itself a therapeutic protein, or additional antigenic characteristics.

20           Another desirable protein of this invention may comprise a complete antibody molecule, having full length heavy and light chains, or any discrete fragment thereof, such as the Fab or F(ab')<sub>2</sub> fragments, a heavy chain dimer, or any minimal recombinant fragments thereof such as an F<sub>v</sub> or a single-chain antibody (SCA) or any other molecule with the same specificity as the selected donor mAb. Such protein may be used in the form of an altered antibody, or may be used in its unfused form.

25           Whenever the second immunoglobulin partner is derived from an antibody different from the donor antibody, e.g., any isotype or class of immunoglobulin framework or constant regions, an engineered antibody results. Engineered antibodies can comprise immunoglobulin (Ig) constant regions and variable framework regions from one source, e.g., the acceptor antibody, and one or more (preferably all) CDRs from the donor antibody. In addition, alterations, e.g., deletions, substitutions, or additions, of the acceptor mAb light and/or heavy variable domain framework region at the nucleic acid or amino acid levels, or the donor CDR regions may be made in order to retain donor antibody antigen binding specificity.

5        Such engineered antibodies are designed to employ one (or both) of the variable heavy and/or light chains of the anti-MAG mAb or one or more of the heavy or light chain CDRs. The engineered antibodies may be neutralising, as above defined.

10       It will be understood by those skilled in the art that the humanised antibody may be further modified by changes in variable domain amino acids without necessarily affecting the specificity and high affinity of the donor antibody (i.e., an analog). It is anticipated that heavy and light chain amino acids may be substituted by other amino acids either in the variable domain frameworks or CDRs or both.

15       In addition, the constant region may be altered to enhance or decrease selective properties of the molecules of the instant invention. For example, dimerization, binding to Fc receptors, or the ability to bind and activate complement (see, e.g., Angal et al., Mol. Immunol., 30:105-108 (1993), Xu et al., J. Biol. Chem., 269:3469-3474 (1994), Winter et al., EP 307,434-B).

20       Preferably, the variable light and/or heavy chain sequences and the CDRs of suitable donor mAbs, and their encoding nucleic acid sequences, are utilized in the construction of the humanized antibodies, of this invention, by the following process. The same or similar techniques may also be employed to generate other embodiments of this invention.

25       A hybridoma producing a selected donor mAb is conventionally cloned, and the DNA of its heavy and light chain variable regions obtained by techniques known to one of skill in the art; e.g., the techniques described in Sambrook et al., (Molecular Cloning (A Laboratory Manual)), 2nd edition, Cold Spring Harbor Laboratory (1989)). The variable heavy and light regions containing at least the CDR-encoding regions and those portions of the acceptor mAb light and/or heavy variable domain framework regions required in order to retain donor mAb binding specificity, as well as the remaining immunoglobulin-derived parts of the antibody chain derived from a human immunoglobulin are obtained  
30       using polynucleotide primers and reverse transcriptase. The CDR-encoding regions are identified using a known database and by comparison to other antibodies.

35       A mouse/human chimeric antibody may then be prepared and assayed for binding ability. Such a chimeric antibody contains the entire non-human donor antibody V<sub>H</sub> and V<sub>L</sub> regions, in association with human Ig constant regions for both chains.

5 Homologous framework regions of a heavy chain variable region from a human antibody may be identified using computerized databases, e.g., KABAT®, and a human antibody having homology to the donor antibody will be selected as the acceptor antibody. A suitable light chain variable framework region can be designed in a similar manner.

10 A humanized antibody may be derived from the chimeric antibody, or preferably, made synthetically by inserting the donor mAb CDR-encoding regions from the heavy and light chains appropriately within the selected heavy and light chain framework. Alternatively, a humanized antibody can be made using standard mutagenesis techniques. Thus, the resulting humanized antibody contains human framework regions and donor  
15 mAb CDR-encoding regions. There may be subsequent manipulation of framework residues. The resulting humanized antibody can be expressed in recombinant host cells, e.g., COS, CHO or myeloma cells.

A conventional expression vector or recombinant plasmid is produced by placing these coding sequences for the antibody in operative association with conventional  
20 regulatory control sequences capable of controlling the replication and expression in, and/or secretion from, a host cell. Regulatory sequences include promoter sequences, e.g., CMV promoter, and signal sequences, which can be derived from other known antibodies. Similarly, a second expression vector can be produced having a DNA sequence which encodes a complementary antibody light or heavy chain. Preferably this second  
25 expression vector is identical to the first except insofar as the coding sequences and selectable markers are concerned, so to ensure as far as possible that each polypeptide chain is functionally expressed. Alternatively, the heavy and light chain coding sequences for the altered antibody may reside on a single vector.

A selected host cell is co-transfected by conventional techniques with both the  
30 first and second vectors (or simply transfected by a single vector) to create the transfected host cell of the invention comprising both the recombinant or synthetic light and heavy chains. The transfected cell is then cultured by conventional techniques to produce the engineered antibody of the invention. The humanized antibody which includes the association of both the recombinant heavy chain and/or light chain is  
35 screened from culture by appropriate assay, such as ELISA or RIA. Similar conventional techniques may be employed to construct other altered antibodies and molecules.

5           Suitable vectors for the cloning and subcloning steps employed in the methods and construction of the compositions of this invention may be selected by one of skill in the art. For example, the conventional pUC series of cloning vectors, may be used. One vector, pUC19, is commercially available from supply houses, such as Amersham (Buckinghamshire, United Kingdom) or Pharmacia (Uppsala, Sweden). Additionally, any  
10       vector which is capable of replicating readily, has an abundance of cloning sites and selectable genes (e.g., antibiotic resistance), and is easily manipulated may be used for cloning. Thus, the selection of the cloning vector is not a limiting factor in this invention.

          Similarly, the vectors employed for expression of the antibodies may be selected by one of skill in the art from any conventional vector. The vectors also contain selected  
15       regulatory sequences (such as CMV promoters) which direct the replication and expression of heterologous DNA sequences in selected host cells. These vectors contain the above described DNA sequences which code for the antibody or altered immunoglobulin coding region. In addition, the vectors may incorporate the selected immunoglobulin sequences modified by the insertion of desirable restriction sites for ready manipulation.

20       The expression vectors may also be characterized by genes suitable for amplifying expression of the heterologous DNA sequences, e.g., the mammalian dihydrofolate reductase gene (DHFR). Other preferable vector sequences include a poly A signal sequence, such as from bovine growth hormone (BGH) and the betaglobin promoter sequence (betaglopro). The expression vectors useful herein may be synthesized by  
25       techniques well known to those skilled in this art.

          The components of such vectors, e.g. replicons, selection genes, enhancers, promoters, signal sequences and the like, may be obtained from commercial or natural sources or synthesized by known procedures for use in directing the expression and/or secretion of the product of the recombinant DNA in a selected host. Other appropriate  
30       expression vectors of which numerous types are known in the art for mammalian, bacterial, insect, yeast, and fungal expression may also be selected for this purpose.

          The present invention also encompasses a cell line transfected with a recombinant plasmid containing the coding sequences of the antibodies or altered immunoglobulin molecules thereof. Host cells useful for the cloning and other manipulations of these  
35       cloning vectors are also conventional. However, most desirably, cells from various strains

5 of *E. coli* are used for replication of the cloning vectors and other steps in the construction of altered antibodies of this invention.

Suitable host cells or cell lines for the expression of the antibody of the invention are preferably mammalian cells such as N20, Sp2/0, CHO, COS, a fibroblast cell (e.g., 3T3), and myeloid cells, and more preferably a CHO or a myeloid cell. Human cells may be used,  
10 thus enabling the molecule to be modified with human glycosylation patterns. Alternatively, other eukaryotic cell lines may be employed. The selection of suitable mammalian host cells and methods for transformation, culture, amplification, screening and product production and purification are known in the art. See, e.g., Sambrook *et al.*, cited above.

15 Bacterial cells may prove useful as host cells suitable for the expression of the recombinant Fabs of the present invention (see, e.g., Plückthun, A., *Immunol. Rev.*, 130:151-188 (1992)). However, due to the tendency of proteins expressed in bacterial cells to be in an unfolded or improperly folded form or in a non-glycosylated form, any recombinant Fab produced in a bacterial cell would have to be screened for retention of  
20 antigen binding ability. If the molecule expressed by the bacterial cell was produced in a properly folded form, that bacterial cell would be a desirable host. For example, various strains of *E. coli* used for expression are well-known as host cells in the field of biotechnology. Various strains of *B. subtilis*, *Streptomyces*, other bacilli and the like may also be employed in this method.

25 Where desired, strains of yeast cells known to those skilled in the art are also available as host cells, as well as insect cells, e.g. *Drosophila* and *Lepidoptera* and viral expression systems. See, e.g. Miller *et al.*, *Genetic Engineering*, 8:277-298, Plenum Press (1986) and references cited therein.

The general methods by which the vectors may be constructed, the transfection  
30 methods required to produce the host cells of the invention, and culture methods necessary to produce the altered antibody of the invention from such host cell are all conventional techniques. Likewise, once produced, the antibodies of the invention may be purified from the cell culture contents according to standard procedures of the art, including ammonium sulfate precipitation, affinity columns, column chromatography, gel  
35 electrophoresis and the like. Such techniques are within the skill of the art and do not

- 5 limit this invention for example, preparation of humanised antibodies is described in WO 99/58679.

Yet another method of expression of the antibodies may utilize expression in a transgenic animal, such as described in U. S. Patent No. 4,873,316. This relates to an expression system using the animal's casein promoter which when transgenically  
10 incorporated into a mammal permits the female to produce the desired recombinant protein in its milk.

- Once expressed by the desired method, the antibody is then examined for *in vitro* activity by use of an appropriate assay. Presently conventional ELISA assay formats are employed to assess qualitative and quantitative binding of the antibody to MAG.
- 15 Additionally, other *in vitro* assays may also be used to verify neutralizing efficacy prior to subsequent human clinical studies performed to evaluate the persistence of the antibody in the body despite the usual clearance mechanisms.

- The therapeutic agents of this invention may be administered as a prophylactic or post injury, or as otherwise needed. The dose and duration of treatment relates to the  
20 relative duration of the molecules of the present invention in the human circulation, and can be adjusted by one of skill in the art depending upon the condition being treated and the general health of the patient.

- The mode of administration of the therapeutic agent of the invention may be any suitable route which delivers the agent to the host. The antagonists and antibodies, and  
25 pharmaceutical compositions of the invention are particularly useful for parenteral administration, i.e., subcutaneously, intramuscularly, intravenously, or intranasally.

- Therapeutic agents of the invention may be prepared as pharmaceutical compositions containing an effective amount of the antagonist or antibody of the invention as an active ingredient in a pharmaceutically acceptable carrier. In the  
30 prophylactic agent of the invention, an aqueous suspension or solution containing the engineered antibody, preferably buffered at physiological pH, in a form ready for injection is preferred. The compositions for parenteral administration will commonly comprise a solution of the antagonist or antibody of the invention or a cocktail thereof dissolved in an pharmaceutically acceptable carrier, preferably an aqueous carrier. A variety of  
35 aqueous carriers may be employed, e.g., 0.9% saline, 0.3% glycine, and the like. These solutions are sterile and generally free of particulate matter. These solutions may be

5 sterilized by conventional, well known sterilization techniques (e.g., filtration). The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and buffering agents, etc. The concentration of the antagonist or antibody of the invention in such pharmaceutical formulation can vary widely, i.e., from less than about 0.5%, usually at or at least about  
10 1% to as much as 15 or 20% by weight and will be selected primarily based on fluid volumes, viscosities, etc., according to the particular mode of administration selected.

Thus, a pharmaceutical composition of the invention for intramuscular injection could be prepared to contain 1 mL sterile buffered water, and between about 1 ng to about 100 mg, e.g. about 50 ng to about 30 mg or more preferably, about 5 mg to about  
15 25 mg, of an antagonist or antibody of the invention. Similarly, a pharmaceutical composition of the invention for intravenous infusion could be made up to contain about 250 ml of sterile Ringer's solution, and about 1 to about 30 and preferably 5 mg to about 25 mg of an engineered antibody of the invention. Actual methods for preparing parenterally administrable compositions are well known or will be apparent to those  
20 skilled in the art and are described in more detail in, for example, Remington's Pharmaceutical Science, 15th ed., Mack Publishing Company, Easton, Pennsylvania.

It is preferred that the therapeutic agent of the invention, when in a pharmaceutical preparation, be present in unit dose forms. The appropriate therapeutically effective dose can be determined readily by those of skill in the art. To  
25 effectively treat stroke and other neurological diseases in a human, one dose of up to 700 mg per 70 kg body weight of an antagonist or antibody of this invention should be administered parenterally, preferably *i.v.* or *i.m.* (intramuscularly). Such dose may, if necessary, be repeated at appropriate time intervals selected as appropriate by a physician.

30 The antibodies described herein can be lyophilized for storage and reconstituted in a suitable carrier prior to use. This technique has been shown to be effective with conventional immunoglobulins and art-known lyophilization and reconstitution techniques can be employed.

In another aspect, the invention provides a pharmaceutical composition  
35 comprising anti-MAG antibody of the present invention or a functional fragment thereof



- 5 and a pharmaceutically acceptable carrier for treatment or prophylaxis of stroke and other neurological diseases.

In a yet further aspect, the invention provides a pharmaceutical composition comprising the anti-MAG antibody of the present invention or a functional fragment thereof and a pharmaceutically acceptable carrier for inhibiting neurodegeneration  
10 and/or promoting functional recovery in a human patient suffering, or at risk of developing, a stroke or other neurological disease.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any novel feature or combination of features described  
15 herein. This may take the form of product, composition, process or use claims and may include, by way of example and without limitation, one or more of the following claims.

5

CLAIMS

1. A humanised antibody or functional fragment thereof that binds to and neutralises MAG which comprises a heavy chain variable region comprising the following amino acid sequence

10

QVQLVQSGSELKKPGASVKVSCKASGYTFTNYGMNWVRQAPGQGLEWMGWI  
NTYTGEPTYADDFTGRFVFSLDTSVSTAYLQISSLKAEDTAVYYCARNPIN  
YGINYEGYVMDYWGQGLTVTVSS (SEQ ID No 1).

15

2. A humanised antibody or functional fragment thereof which binds to MAG which comprises the heavy chain variable region of Sequence ID No 1 together with a light chain variable region comprising amino acid Sequence ID No 2,3,4 or 5:

20

DIVMTQSPDSLAVSLGERATINCSSHSVLYSSNQKNYLAWYQQKPGQPPK  
 LLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCHQYLSSLT  
 FGQGTKLEIKRTV (SEQ ID No 2)

25

DIVMTQSPDSLAVSLGERATINCSSHSVLYSSNQKNYLAWYQQKPGQPPK  
 LLIYWASTRESGVPDRFSGSGSGTDFTLTIINLQAEDVAVYYCHQYLSSLT  
 FGQGTKLEIKRTV (SEQ ID No 3)

30

DIVMTQSPDSLAVSLGERATINCSSHSVLYSSNQKNYLAWYQQKPGQPPK  
 LLIYWASTRESGVPDRFSGSGSGTDFTLTISSLHTEDVAVYYCHQYLSSLT  
 FGQGTKLEIKRTV (SEQ ID No 4)

35

3. A humanised antibody comprising:  
 a heavy chain variable fragment comprising SEQ ID No 1 and a constant part of fragment thereof of a human heavy chain  
 and  
 a light chain variable fragment comprising SEQ ID No 2, 3, 4 or 5 and a constant part or fragment thereof of a human light chain.

40

- 5
4. A humanised antibody according to claims 1-3 wherein the light chain variable region is SEQ ID No 2.
- 10
5. A humanised antibody according to claims 1-3 wherein the light chain variable region is SEQ ID No. 3.
6. A humanised antibody according to claims 1-3 wherein the light chain variable region is SEQ ID No 4.
- 15
7. A humanised antibody according to claims 1-3 wherein the light chain variable region is SEQ ID No. 5.
8. A pharmaceutical composition comprising an altered anti-MAG antibody or functional fragment thereof according to claims 1-7 together with a
- 20
- pharmaceutically acceptable diluent or carrier.
9. A method of treatment or prophylaxis of stroke and other neurological diseases in a human which comprises administering to said human in need thereof an effective amount of an anti-MAG antibody, according to claims 1-7 or a
- 25
- functional fragment thereof.
10. The use of an anti-MAG antibody according to claims 1-7 or a functional fragment thereof in the preparation of a medicament for treatment or prophylaxis of stroke and other neurological diseases.
- 30
11. A method of inhibiting neurodegeneration and/or promoting functional recovery in a human patient suffering, or at risk of developing, a stroke or other neurological disease which comprises administering to said human in need thereof an effective amount of an anti-MAG antibody according to claims 1-7 or a
- 35
- functional fragment thereof.

- 5 12. The use of an anti-MAG antibody according to claims 1-7, or a functional fragment thereof in the preparation of a medicament for inhibiting neurodegeneration and/or promoting functional recovery in a human patient suffering from, or at risk of developing, a stroke and other neurological disease.

Abstract

The present invention relates to humanised antibodies to myelin associated glycoprotein (MAG), pharmaceutical formulations containing them and to the use of such antibodies in the treatment and/or prophylaxis of neurological diseases.

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